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Randomized Phase II Trial of Bevacizumab plus Everolimus versus Bevacizumab Alone for Recurrent or Persistent Ovarian, Fallopian Tube or Peritoneal Carcinoma: an NRG Oncology/ Gynecologic Oncology Group Study

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AUTHOR CONTRIBUTIONS

All authors provided data, were involved in design, analysis, writing, revision, and approved the final manuscript. Dr. Michael Sill performed the statistical analyses of this study.

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Abstract

Purpose: Bevacizumab (BV) monotherapy leads to compensatory upregulation of multiple signaling pathways, resulting in mTOR activation. We evaluated combining BV and everolimus (EV), an mTOR kinase inhibitor, to circumvent BV-resistance in women with recurrent or persistent ovarian, fallopian tube or primary peritoneal cancer (OC).

Patients and Methods: Eligible OC patients had measurable (RECIST1.1) or detectable disease, 1–3 prior regimens, performance status (PS) 0–2, and no prior m-TOR inhibitor. All patients received BV 10 mg/kg IV every 2wks. Patients were randomized (1:1) to oral EV (10 mg daily) or placebo stratified by platinum-free interval (PFI), measurable disease and prior BV. Primary endpoint was progression-free survival (PFS); secondary endpoints included safety and response.

Results: 150 patients were randomized to BV with (n=75) and without (n=75) EV. Arms were well-balanced for age (median 63: range 28–92), PS (0: 73%, 1–2: 27%), prior regimens (1: 37%, 2: 47%, 3: 16%), prior BV (11%), PFI (<6mos: 65%) and measurable disease (81%). The BV+EV vs BV median PFS was 5.9 vs 4.5 months (hazard ratio [HR] 0.95 (95% CI, 0.66–1.37, p=0.39)). Median OS was 16.6 vs 17.3 months (HR 1.16 (95% CI, 0.72~1.87, p=0.55)). Objective measurable responses were higher with BV+EV (22% vs 12%). Study removal due to toxicity was higher with BV+EV (29% vs 12%). Toxicity (grade 3) from BV+EV were “other GI (mucositis)” (23 vs 1%) and “metabolic/nutrition” (19 vs. 7%); common ≥ grade 2 toxicities with BV+EV were cytopenia, nausea, fatigue and rash.

Conclusion: The combination regimen (BV+EV) did not significantly reduce the hazard of progression or death relative to BV and was associated with higher rates of adverse events and study discontinuation when compared to BV alone.

Keywords

Ovarian Cancer; Bevacizumab; Everolimus; Targeted Therapy

INTRODUCTION

Anti-vascular endothelial growth factor (VEGF) treatments have been shown to be an effective strategy for controlling tumor growth in ovarian cancer (OC) via the angiogenic and other growth pathways.^{1–3} Bevacizumab (BV), a recombinant humanized monoclonal antibody against VEGF, has clinical activity as both a single agent and in combination with cytotoxic chemotherapy.^{4–12} Based on improved progression-free survival (PFS) and overall survival (OS) in certain populations, bevacizumab is indicated in both platinum-resistant and

platinum-sensitive recurrent ovarian cancer and in conjunction with platinum-based therapy in upfront treatment.

Everolimus, a rapalog-type inhibitor of mammalian target of rapamycin (mTOR) complex 1 (mTORC1), attenuates up regulation of HIF-1 α levels, a resistance mechanism for antiangiogenics, and targets the PI3-Kinase/AKT/mTOR axis, commonly aberrant in OC.^{13–16} Everolimus (Afinitor, Novartis) has indications in advanced renal cell carcinoma (RCC), well-differentiated advanced neuroendocrine tumors (NET), advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane, and renal angiomyolipoma and tuberous sclerosis complex.¹⁷

The Ovarian Carcinoma Cancer Genome Atlas Research Network identified PI3K/RAS pathway deregulation in 45% ovarian cases.¹⁸ Single agent rapalog trials in recurrent ovarian cancer have yielded modest results. The Gynecologic Oncology Group (GOG) performed a study of temsirolimus showing a response rate (RR) of 9.3% (5/54 patients), with 24.1% of patients progression-free at 6 months.¹⁹ A similar study, performed by the AGO study group (AGO-GYN8) yielded a response rate of 4.5% (1/22 patients).²⁰

Targeted therapy combinations that include blocking VEGF and other cancer growth pathways may circumvent resistance to angiogenesis inhibition and be more tolerable and effective compared to traditional cytotoxic combinations. Everolimus has been safely combined with bevacizumab and studied in a non-randomized phase 2 trial in advanced RCC.^{21–22} A phase 1 trial of bevacizumab and temsirolimus was performed in gynecologic malignancies showing safe delivery of full doses of both agents and a response rate of 17% (7/41 patients).²³

The objective of this study was to assess PFS in a randomized phase II study of bevacizumab alone (with an oral placebo) versus the combination of bevacizumab and oral everolimus among women with recurrent epithelial ovarian cancer.

Patients and Methods:

The study was designed as a double-blind, placebo-controlled prospective randomized phase II trial of intravenous (IV) bevacizumab every 2 weeks in combination with either oral everolimus or an oral placebo (Gynecologic Oncology Group protocol 186-G; [ClinicalTrials.gov](https://clinicaltrials.gov). Identifier: NCT00886691).

Eligible patients included women older than 18 years of age with a GOG performance status of 0–2. All patients were required to have measurable (per RECIST 1.1) or detectable disease from persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Detectable disease required at least one of the following conditions: baseline values of cancer antigen (CA)-125 at least 2 \times upper-limit-of normal (ULN), ascites and/or pleural effusion attributed to tumor, or solid and/or cystic abnormalities on radiographic imaging that do not meet RECIST 1.1 definitions for target lesions. Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease and were allowed to receive up to two additional cytotoxic regimens for management of recurrent or persistent disease, with no more than 1 non-platinum, non-taxane regimen.

Patients who have had one prior treatment must have had a GOG Performance Status of 0, 1, or 2; patients who have had two or three prior treatments must have had a GOG Performance Status of 0 or 1. Patients were allowed to receive biologic (non-cytotoxic) therapy, including VEGF blockade, as part of their primary treatment regimen, but not for recurrent or persistent disease. Patients with either platinum-sensitive (platinum-free interval (PFI) >182 days) or platinum-resistant (PFI ≤182 days) disease were eligible. Patients who received only one prior cytotoxic regimen must have had a PFI ≥365 days or had progressed during platinum-based therapy, or had persistent disease after a platinum-based therapy.

Adequate laboratory studies included 1- bone marrow function defined as absolute neutrophil count (ANC) ≥1,500/mcl, platelets ≥100,000/mcl; 2- renal function defined as creatinine ≤1.5 × institutional ULN; 3- hepatic function defined as bilirubin ≤1.5 × ULN, SGOT (AST) ≤3 × ULN and alkaline phosphatase ≤2.5 × ULN; 4- blood coagulation parameters with PT such that international normalized ratio (INR) was ≤1.5 (or an in-range INR, usually between 2 and 3, if a patient was on a stable dose of therapeutic warfarin for management of deep vein thrombosis including pulmonary embolism) and a PTT ≤1.5 times the upper limit of normal; 5- fasting serum cholesterol ≤300 mg/dL OR ≤7.75 mmol/L AND fasting triglycerides ≤300 mg/dL OR ≤3.42 mmol/L; 6- Urine protein creatinine (UPC) ratio must have been <1.0 gm. If UPC ratio was ≥1, collection of 24-hour urine measurement of urine protein was recommended. UPC ratio of spot urine is an estimation of the 24-hour urine protein excretion - a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm.

Patients were excluded if they had significant comorbidities including acute hepatitis, active infection requiring parenteral antibiotics, active bleeding (or bleeding disorder), CNS disease (including uncontrolled seizures, brain metastasis and history of cerebrovascular accident or bleed within six months of study treatment), cardiovascular disease (uncontrolled hypertension, defined as systolic >150 mm Hg or diastolic >90 mm Hg, myocardial infarction or unstable angina within six months prior to registration, New York Heart Association (NYHA) Class II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, prior treatment with an anthracycline and had an ejection fraction <50%, or CTCAE Grade 2 or greater peripheral vascular disease), signs of gastrointestinal obstruction (including patients who require parenteral hydration and/or nutrition), serious wounds, abscess, or bowel perforation. Patients with prior recent invasive malignancies and those not recovered from the effects of recent surgery, radiotherapy, or chemotherapy were excluded. Patients of childbearing potential were required to have a negative serum pregnancy test before entering the study and were required to practice an effective form of contraception.

Any other prior therapy directed at the malignant tumor, including biological and immunologic agents, had to be discontinued at least three weeks prior to registration (including small molecules and murine monoclonal antibodies). Chimeric, human, or humanized monoclonal antibodies (including bevacizumab) or VEGF receptor fusion protein (including VEGF Trap, aflibercept) had to be discontinued for at least 12 weeks prior to registration. No investigational therapy within 30 days prior to the first date of study

treatment was allowed and patients who had received prior everolimus or any other mTOR inhibitor were excluded.

All patients signed an approved informed consent and authorization permitting the release of personal health information.

Blinding

Blinding was employed to help preserve the integrity of the PFS and OS endpoints by eliminating biases in disease assessment monitoring, the declaration of disease progression and the institution/selection of future therapies. Therefore, it was understood that investigators, patients and research personnel would not know if patients have received everolimus or placebo.

Drug Administration and Supportive Care

Bevacizumab was administered at 10 mg/kg as a continuous intravenous (IV) infusion once every two weeks. The dose was based on the patient's actual body weight and only recalculated if there was a weight change of >10% from baseline. The initial dose was administered over 90 minutes. If no adverse reactions occurred after the initial dose, the second dose was administered over 60 minutes. If no adverse reactions occurred after the second dose, all subsequent doses were administered over 30 minutes. If infusion-related adverse reactions occurred at any time, subsequent doses of bevacizumab were administered over the shortest period that was well tolerated. Routine premedication was not required for the first dose of bevacizumab. If infusion reactions occurred, diphenhydramine, dexamethasone and an H1 blocker were administered as premedication. IV bevacizumab was administered before the oral dose of everolimus or placebo.

Everolimus or placebo was dispensed as tablets at the beginning of each treatment cycle (day 1, every 4 weeks). All dosages were prescribed and dispensed to the patient and all dose changes during the study were recorded. Everolimus or placebo was administered orally as a once-daily dose of 10 mg (two 5 mg tablets) continuously from study day 1 until progression of disease or unacceptable toxicity. Patients were instructed to take everolimus or placebo in the morning, at the same time each day. Everolimus or placebo was taken by the patient in a fasting state or with no more than a light fat-free meal. Dietary habits around the time of tablet intake were kept as consistent as possible throughout the study and if applicable, no attempt to replace the vomited dose.

Prior to each IV treatment, special attention was given to known bevacizumab effects: blood pressure, proteinuria, bleeding, cardiovascular events and bowel perforation. Type of blood pressure medications was administered at the discretion of the investigator.

For the oral everolimus or placebo, nausea and vomiting were managed at the investigator discretion with guidelines given for interacting medications. Diarrhea was managed with loperamide. Mild mucositis treated with conservative measures such as non-alcoholic and/or salt water (0.9%) mouth wash; more severe mucositis required topical analgesic and/or topical corticosteroid mouth treatments. Significant fasting hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or hypertriglyceridemia (>300 mg/dL or >3.42 mmol/L) were

treated with a statin or appropriate lipid-lowering medication in addition to diet. Patients with diabetes were instructed to monitor glucose levels closely and may alter insulin and/or oral hypoglycemic therapy requirements. To avoid drug interactions, patients were instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. Concurrent administration of everolimus and strong or moderate CYP3A4 inhibitors, strong CYP3A4 inducers and strong and moderate inhibitors of P-glycoprotein (PgP) were avoided.

Dose Modifications

Dose reductions were not allowed for bevacizumab. Interruption of bevacizumab was mandated for certain adverse events (grade 2 symptomatic hypertension, grade 3 thromboembolic events or hypertension, >3.5gm proteinuria over 24 hours, grade 3 hemorrhage) with intervention guidelines and parameters to restart. Bevacizumab was discontinued permanently for grade 2 arterial thromboembolic events or intracranial/pulmonary hemorrhage; grade >3 AE, including allergic infusion reactions and wound complications; any grade 4 including symptomatic venous thromboembolic events, hypertension, and hemorrhage. Any grade of posterior reversible encephalopathy syndrome (PRES), wound dehiscence, perforation, fistula or nephrotic syndrome (or persistent proteinuria >3.5 gm) required discontinuation of bevacizumab. If bevacizumab was interrupted for toxicity, everolimus or placebo could continue. Patients were removed from the study if bevacizumab was not given for greater than 8 weeks. If everolimus or placebo was interrupted for any reason for >3 weeks, oral therapy was discontinued; however patients could continue on the study with bevacizumab alone.

Dose reductions were allowed with everolimus or placebo (initial dose 10mg; level 1 dose reduction at 5 mg daily; level 2 dose reduction at 5 mg every other day). Persistent (>24 hours) grade 3 non-hematologic toxicity in spite of optimal medical management required reduction of one dose level and delay in subsequent therapy for a maximum of three weeks until recovered to grade 1. Grade 2 (symptomatic) and grade 3 pneumonitis required corticosteroid administration. Everolimus or placebo was discontinued for any grade 4 AE, treatment hold for >3 weeks, or related adverse events requiring dose modification despite two previous dose reductions.

Study Endpoints

Tumor measurements using (computed tomography or magnetic resonance imaging) were made once during every other 4-week cycle according to RECIST 1.1 for the first six months and then every 3 cycles thereafter; and at any other time if clinically indicated based on symptoms or physical signs suggestive of progression of disease or rising serum CA-125 tumor markers. For those with measurable disease, progression (PD) was defined as at least a 20% increase in the sum of the diameters of the target lesions, taking as reference the smallest sum on the study. In addition to the relative increase of at least 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions or unequivocal progression of non-target lesions was also considered PD. Partial response was defined as at least a 30% decrease in the sum of the diameters of target lesions from the baseline sum. Complete response was defined as the disappearance of all target and

non-target lesions and no new lesions. Stable disease was any condition not meeting the above criteria. Responses required confirmation on repeat imaging at greater than or equal to 4 weeks from initial documentation.

For those with detectable but non-measurable disease, assessment was based on CA-125, malignant fluid (i.e. ascites or pleural effusion), and/or evaluation of indeterminate solid or cystic abnormalities. CA-125 responses, regardless of measurable status, were assessed with Rustin criteria.²⁷ Initial values within two weeks of starting therapy had to be 2x ULN to be considered evaluable. At least a 50% reduction in CA-125 levels from the baseline value was maintained for at least 28 days represented a partial response. A full response was defined as normalization (less than ULN) of CA-125 levels that maintained normal for at least 28 days. The date of progression by CA-125 level was determined by values ≥ 2 x maximum (ULN, nadir) that was confirmed at least eight days later. If the date of progression was within eight weeks, PD was entered. If patients had evaluations more than eight weeks from study entry without PD, then their response was at least stable disease. Patients were evaluated by using best overall response while receiving study therapy.

Statistical Design

The primary objective of this study was to estimate the PFS hazard ratio (HR) of the combination of oral everolimus and bevacizumab to oral placebo and bevacizumab. The study was powered to detect a true 37.5% reduction in the hazard ratio of PFS by using the Cox proportional hazards model. The target enrollment was 150 patients (75 per arm) with 123 events to achieve 90% power with a 10% level of significance when conducted with an interim analysis (at approximately the 62nd event) using the method provided by Wei and et al. that rejected the study drug when the $HR > 1$.²⁴ There was no suspension of study accrual during the interim analysis. The final analysis involving efficacy used the intent to treat principle and occurred at approximately the 123rd event (taken from both arms).²⁵ Secondary objectives included 1) to estimate and compare the nature and degree of toxicity of oral everolimus (or placebo) plus bevacizumab, 2) to characterize and compare PFS and OS in patients with measurable disease (RECIST criteria) and patients with detectable (non-measurable) disease, 3) to estimate the proportion of patients with measurable disease who have objective tumor responses by treatment, and 4) to provide descriptive information about CA-125 responses by regimen and where possible by objective tumor responses. Estimates of the differences between measurable versus non-measurable disease status on PFS and OS was proposed with plots of survival curves, estimates of quartiles, and hazard ratios where feasible. For everolimus or placebo randomization, patients were stratified according to their platinum-free interval (≤ 182 days versus >182 days), disease status (measurable versus detectable), and prior use of bevacizumab/aflibercept therapy (no use versus prior use).

RESULTS

The study opened on 12/28/2010, was suspended on 3/9/2011 due to problems with unblinding, reopened on 7/18/2011 and was closed to patient entry on 8/14/2012 after the enrollment of 150 patients. During the first 3-month suspension period, there were only 2 patients enrolled. However, a second unblinding occurred later where at least 52 patients in

total were potentially unblinded. The group quickly obtained another distributor of the regimens to avoid further errors. The only ordinary indication for un-blinding was a serious adverse event in which it is determined by the Study Chair that un-blinding would improve patient safety.

The primary outcome data was frozen on 8/26/2013 for the final analysis. All randomly assigned patients were included in the analysis of efficacy (intention to treat). Five patients were never treated (2 in the everolimus experimental arm and 3 in the bevacizumab only arm) and thus, 145 patients were evaluable for toxicity (Figure 1). Patient demographic characteristics are outlined in Table 1 and the two treatment arms were well balanced for age (median 63; range 28–92), PS (0: 73%, 1–2: 27%), prior regimens (1: 37%, 2: 47%, 3: 16%), prior BV (11%), PFI (<6mos: 65%) and measurable disease (81%).

The interim analysis was triggered after 62 PFS events and the final analysis after 127 PFS events. Adding everolimus to bevacizumab did not significantly prolong PFS compared to bevacizumab alone (median PFS 4.5 months for bevacizumab and 5.9 months for bevacizumab plus everolimus; HR, 0.95; with 95% CI, 0.66 to 1.37; one-sided $P=0.39$; Figure 2A). At the time of this data analysis, 73 had died and median follow-up on the bevacizumab alone arm was 15 months and 15.7 months on the everolimus arm. There was no significant difference in OS (median OS 17.3 months for bevacizumab and 16.6 months for bevacizumab plus everolimus; HR, 1.16; with 95% CI, 0.72 to 1.87; two-sided $P=0.55$; Figure 2B).

Among patients with measurable disease, the objective response was about 2x higher with bevacizumab plus everolimus (22% vs 12%; relative probability of responding was 1.84, 95% CI 0.80 to 4.24). Among patients with CA-125 evaluable disease, the CA125 response was about 2x higher response with bevacizumab plus everolimus (27% vs 15%). The odds ratio for radiographic response (experimental to reference) was 2.08 (95% Exact CI 0.71 to 6.60), so although the data favored the experimental regimen through point estimates, the interval estimates were not suggestive of the experimental regimen being superior. The frequency of study removal due to toxicity or patient refusing further treatment was high with the combination regimen (41%) compared to bevacizumab alone (17%). (Table 2) There was no significant association between treatment related death and study regimen. The two patients (one on each treatment arm) who had grade 5 adverse events related to study treatment had a thromboembolism and a hematoma. Sixty-five patients died from progressive disease. Treatment related adverse events are listed in Table 3. The addition of everolimus to bevacizumab was associated with higher toxicities including neutropenia, anemia, thrombocytopenia, nausea, oral mucositis, fatigue, metabolic abnormalities, dyspnea and rash. There were three events of a grade 3–4 gastrointestinal perforation (2%).

DISCUSSION

Bevacizumab has clinical activity as both a single agent and in combination with cytotoxic chemotherapy. Based on the AURELIA trial (AURELIA: A Study of Avastin (bevacizumab) Added to Chemotherapy in Patients with Platinum-resistant Ovarian Cancer), bevacizumab first received approval in the United States in November 2014. By combining chemotherapy

– weekly paclitaxel, liposomal doxorubicin or topotecan – with bevacizumab, the median PFS was improved by 3.3 months (range, 3.4 months to 6.7 months; HR, 0.48; 95% CI, 0.38 to 0.6) and patients reported improvement in disease-related symptoms and quality of life.^{7–8} However, chemotherapy-related toxicities was significant. The GOG created a randomized phase II trial platform (GOG-186 series) to compare non-cytotoxic combinations to single agent targeted agents with the objective to improve the therapeutic ratio of emerging agents in ovarian cancer. A recent study on this GOG-186 series showed promising response and tolerability when combining two antivasculature agents (bevacizumab plus flubretulin) compared to bevacizumab alone.²⁶

Unfortunately, as demonstrated in our trial, everolimus when combined with bevacizumab was an active combination but did not reach the goal of improving PFS or tolerability. This randomized phase II trial comparing bevacizumab alone (plus oral placebo) to bevacizumab plus everolimus did not significantly prolong PFS compared to bevacizumab alone (median PFS 4.5 months for bevacizumab and 5.9 months for bevacizumab plus everolimus; HR, 0.95; with 95% CI, 0.66 to 1.37; one-sided $P=0.39$). However, the regimen was active particularly in women with measurable disease; the objective response (complete or partial response) was two-fold higher with bevacizumab plus everolimus (22% vs 12%). The side effects were considerable and study removal due to toxicity or patient refusing further treatment was high with the combination regimen (41%) compared to bevacizumab alone (17%).

The advantage of this trial was its multicenter and randomized design. The inclusion of a placebo in the design was intended to reduce bias. However, there was an accidental unblinding at several sites due to a distributor error (exposed label of the un-blinding to multiple site pharmacies) and therefore, the power of the placebo inclusion was lost in the final analysis. It is unlikely, however, this had a significant factor to the final conclusions of the study – as most patients on everolimus could easily be determined by the high reports of toxicities compared to the placebo group.

In conclusion, we cannot recommend further exploration of the combination of everolimus and bevacizumab in women with recurrent ovarian cancer.

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RESEARCH HIGHLIGHTS

- Bevacizumab monotherapy is active therapy for recurrent ovarian cancer, but resistance is common
- BV+EV combination had a higher measurable response (22% vs 12%) compared to BV alone
- BV+EV combination had higher toxicity and study removal (29% vs 12%) compared to BV alone
- BV+EV combination did not improve progression free or overall survival

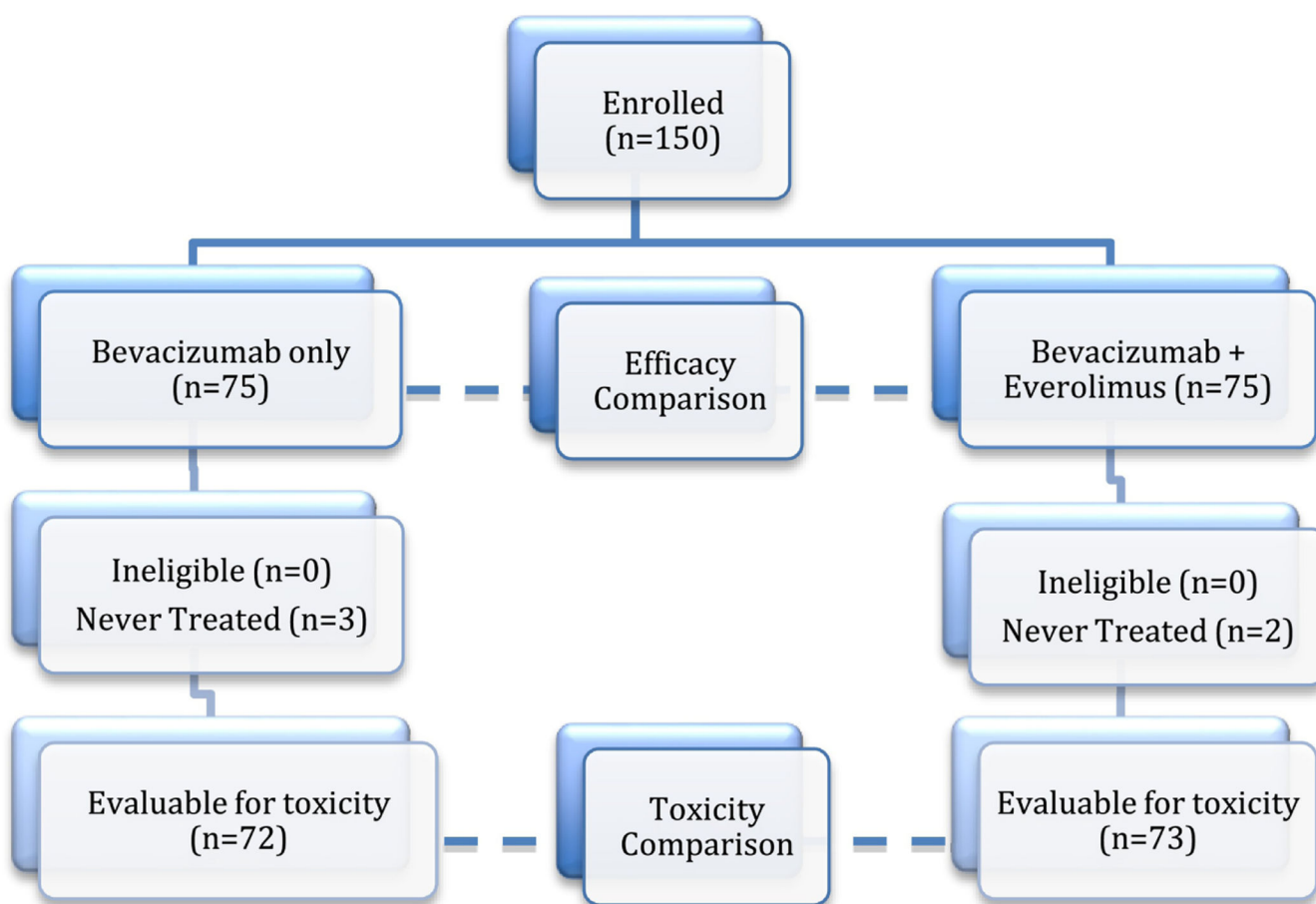
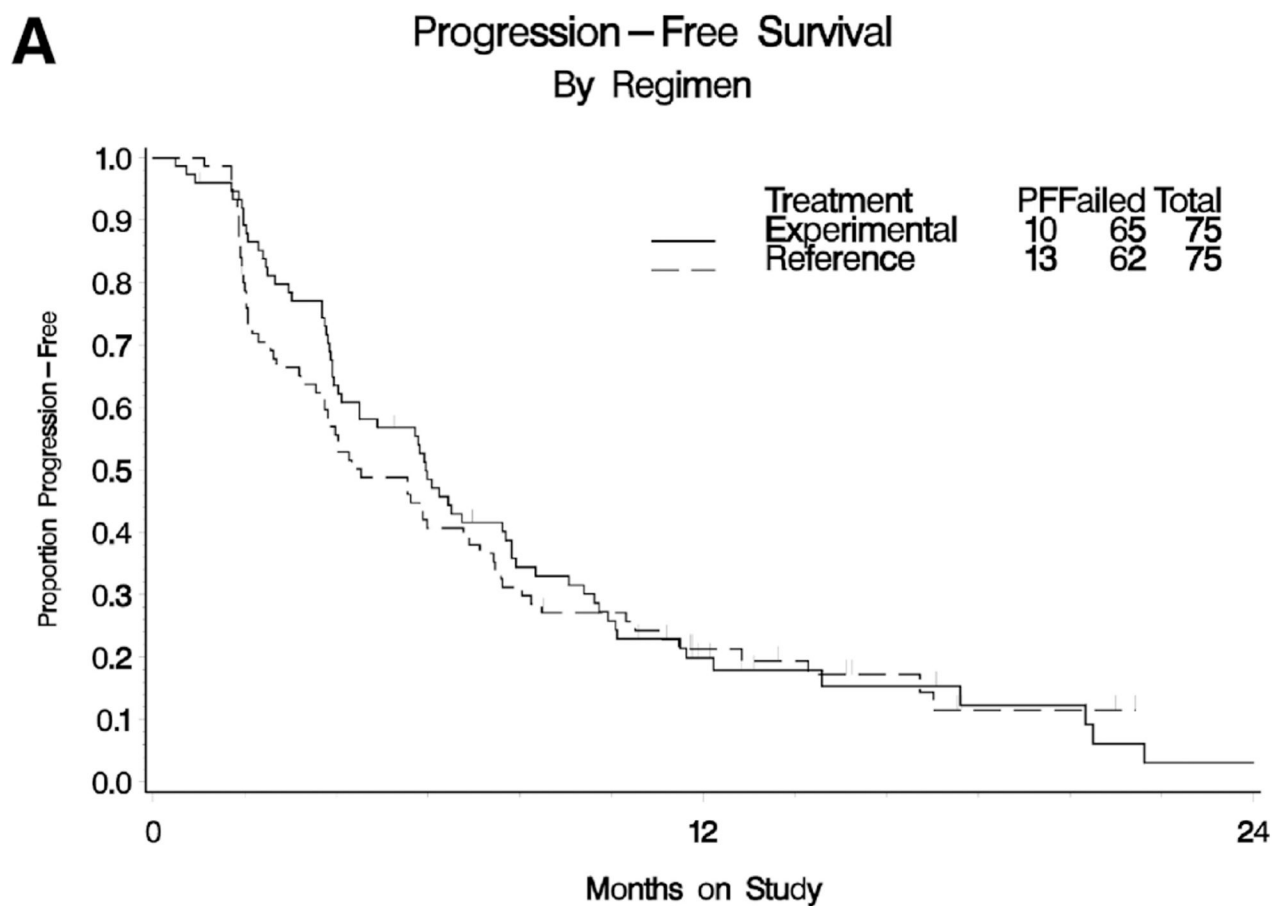
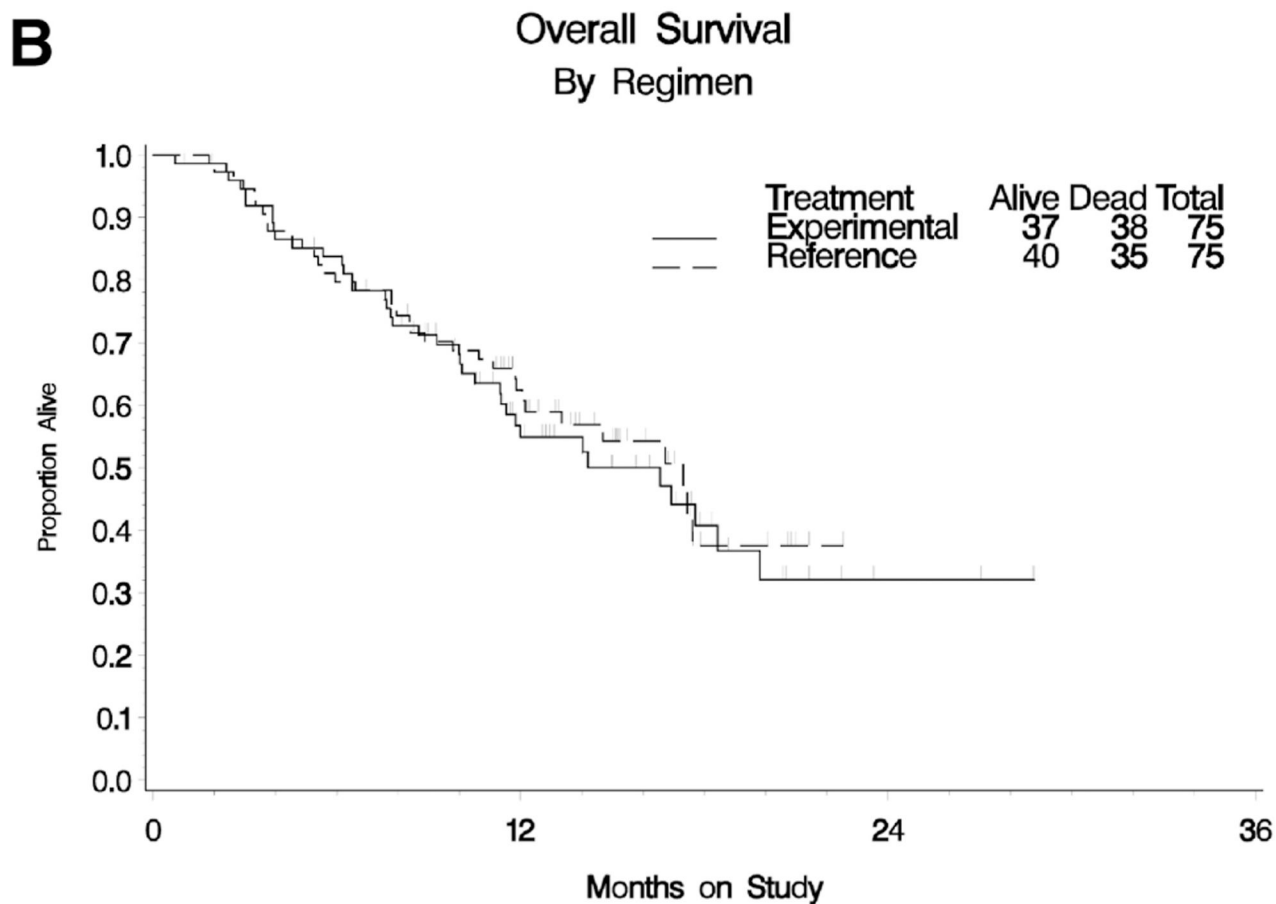


Figure 1:
Study enrollment diagram



Bevacizumab + everolimus had median PFS of 5.9 months (90% CI 4.5 ~7.6)
Bevacizumab alone had median PFS of 4.5 months (90% CI 3.7 ~ 6.0)
Hazard Ratio = 0.96 (95%CI 0.66to 1.37, p=0.39)

Figure 2A:
 Progression-free survival (PFS) analysis by intent to treat.



Bevacizumab + everolimus had median OS of 16.6 months
 Bevacizumab alone had median OS of 17.3 months
 Hazard Ratio = 1.16 (95%CI 0.72 to 1.87, p=0.55)

Figure 2B:
 Overall survival (OS) analysis by intent to treat.

Table 1:**Demographics and Baseline Characteristics**

	Bevacizumab alone		Bevacizumab + Everolimus		TOTAL
	No	%	No	%	
Characteristics					
Age Groups, years					
20–29	1	1.33	0	0	1
30–39	1	1.33	1	1.33	2
40–49	9	12.00	8	10.67	17
50–59	16	21.33	21	28.00	37
60–69	33	44.00	28	37.33	61
70–79	12	16.00	13	17.33	25
>= 80	3	4.00	4	5.33	7
Ethnicity					
Hispanic	1	1.33	2	2.67	3
Non-Hispanic	65	86.67	69	92.00	134
Unknown	9	12.00	4	5.33	13
Race					
Asian	2	2.67	3	4.00	5
African American	6	8.00	3	4.00	9
White	65	86.67	69	92.00	134
Unknown	2	2.67	0	0	2
Performance Status					
0	58	77.33	52	69.33	110
1	17	24.00	21	28.00	38
2	0	2.67	2	2.67	2
Cell Type					
Endometrioid	4	5.33	3	4.00	7
Serous	59	78.67	54	72.00	113
Clear cell	7	9.33	5	6.67	12
Mixed epithelial	3	4.00	4	5.33	7
Undifferentiated	0	0.00	2	2.67	2
Adenocarcinoma, NOS	2	2.67	7	9.33	2
No. of prior regimens					
1	23	32.00	32	42.67	55
2	39	54.67	31	41.33	70
3	13	21.33	12	16.00	25
Prior Radiation					
No	74	98.67	73	97.33	147

	Bevacizumab alone		Bevacizumab + Everolimus		TOTAL
	No	%	No	%	
Characteristics					
Yes	1	1.33	2	2.67	3
Prior Immunotherapy					
No	73	97.33	74	98.67	147
Yes	2	2.67	1	1.33	3
Prior Surgery					
No	5	6.67	1	1.33	6
Yes	70	93.33	74	98.67	144
Prior bevacizumab					
No	66	88.00	68	90.67	134
Yes	9	12.00	7	9.33	16
Measurable disease					
No	12	16.00	17	22.67	29
Yes	63	84.00	58	77.33	121
Platinum interval					
Platinum resistant (<6mo PFI)	47	62.67	51	68.00	98
Platinum sensitive (6 < PFI <12mo)	28	37.33	54	32.00	52
TOTAL (n=150)	75	100%	75	100%	150

Table 2:**Response to Therapy and Patient Outcomes**

	Bevacizumab alone		Bevacizumab + Everolimus		
Characteristics	No.	%	No.	%	Total
Response					
Complete response	0	0	1	1	1
Partial response	7	9	13	17	20
Stable disease	30	40	32	43	62
Progressive disease	16	21	11	15	27
Indeterminate	5	7	6	8	11
Non-measurable	17	23	12	16	29
Alive/cause of death					
Dead from disease	31	41	34	45	65 (43%)
Dead, drug related	0	0	1	1	1 (1%)
Dead, drug-related and disease	1	1	1	1	2 (1%)
Dead, undetermined cause	3	3	2	3	5 (3%)
Alive	40	53	37	49	77(51%)
Reason off study					
Disease progression	49	65	37	49	86 (57%)
Toxicity per protocol	9	12	22	29	31 (21%)
Refused further treatment	4	5	9	12	13 (9%)
Other disease	1	1	2	3	3 (2%)
Other, unknown, or on study	12	16	5	7	17 (12%)

Note: The relative probability of response on the everolimus + bevacizumab arm compared with the bevacizumab alone arm (among patients with measurable disease) was 1.84 (95% CI 0.80–4.24). The odds ratio was 2.08 (95% CI, 0.71–6.60).

Table 3:

Treatment Adverse Events (no. of events)

	Bevacizumab alone (n=72)					Bevacizumab + Everolimus (n=73)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood/Lymphatics										
Neutropenia ¹	5	1	0	0	0	11	15	5	0	0
Anemia ¹	18	5	0	0	0	24	22	1	0	0
Thrombocytopenia ¹	6	2	0	0	0	28	10	1	0	0
Cardiac	1	0	1	0	0	5	1	0	1	0
Ear/labyrinth	2	0	0	0	0	2	20	0	0	0
Gastrointestinal										
Nausea ¹	19	3	4	0	0	13	12	6	0	0
Vomiting	5	4	2	0	0	13	7	5	0	0
Other GI ^{1,2}	34	8	1	0	0	23	22	13	1	0
General/ administrative site ¹	43	9	1	0	0	34	20	7	0	0
Hepatobiliary	0	0	0	0	0	0	2	0	0	0
Immune system	0	0	0	0	0	0	2	0	0	0
Infections	1	6	2	0	0	2	7	6	1	0
Metabolism/nutrition ^{1,2}	18	4	4	1	0	15	14	13	1	0
Musculoskeletal/ connective tissue	24	6	1	0	0	12	8	4	0	0
Nervous system	21	6	2	0	0	28	9	3	0	0
Peripheral neuropathy	10	1	0	0	0	12	1	1	0	0
Other investigations	18	4	2	0	0	18	20	2	0	0
Psychiatric	5	1	0	0	0	8	4	0	0	0
Renal/urinary	7	0	2	0	0	8	5	1	0	0
Respiratory/thoracic ¹	26	3	0	0	0	26	12	4	1	0
Skin/subcutaneous ¹	16	2	0	0	0	24	10	2	0	0
Vascular disorders	7	11	10	2	1	4	7	12	1	1

¹—Toxicities are significantly associated with treatment at the 5% level when classified as mild (Grade <=1), moderate (grade =2) and severe (Grade >=3) (highlighted as a light shadow in table)

²—Toxicities are significantly associated with treatment at the 5% level when classified as mild to moderate and severe (grade 3–5 non-hematologic and grade 4–5 hematologic events) (highlighted as a dark shadow in table)